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[CA/US]; 7340 Ravine Road, Kalamazoo, MI 49009 (US).
RICHARDS, Ivan [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). WARCHOL, Mark, P. [US/US]; 7000 Portage Road, Kalamazoo, MI 49006 (US).

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(74) Agents: KOZLOWSKI, Holly, D., et al.; Dinsmore & Shohl LLP, 1900 Chemed Center, 255 East Fifth Street, Cincinnati, OH 45202 (US).

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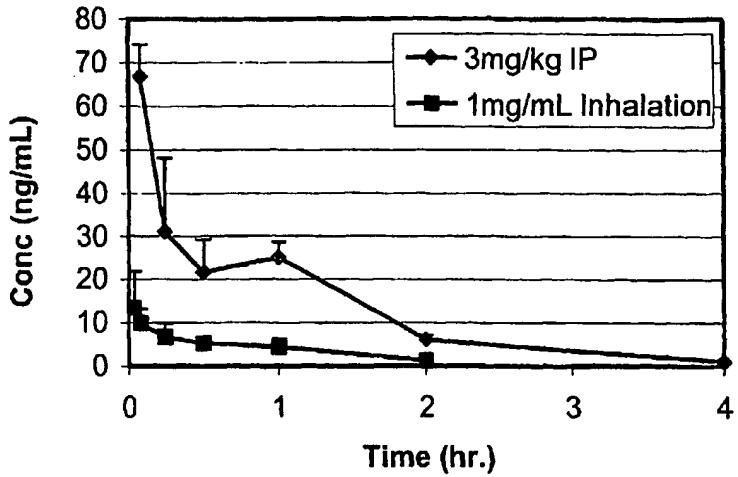
(71) Applicant (for all designated States except US): PHARMACIA & UPJOHN COMPANY [US/US]; 100 Route 206 North, Peapack, NJ 07977 (US).

(72) Inventors; and
(75) Inventors/Applicants (for US only): CAMMARATA, Sue, K. [US/US]; 7000 Portage Road, Kalamazoo, MI 49001 (US). KOLBASA, Karen [US/US]; 301 Henrietta, Kalamazoo, MI 49007 (US). PALANDRA, Joe

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[Continued on next page]

(54) Title: ANTIMUSCARNIC AEROSOL



(57) Abstract: The present invention concerns the use of antimuscarinic agents for the treatment of urinary disorders. The invention provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation. Furthermore, the present invention provides a pharmaceutical composition for treating urinary disorder in a mammal, including man, which is in the form of an inhalable or insufflable preparation and comprises a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor. The invention also provides a novel use of an antimuscarinic agent, or solvate or prodrug thereof, for the manufacture of an inhalable or insufflable medicament for therapeutic treatment of urinary disorders.

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ANTIMUSCARINIC AEROSOL

This application claims the benefit of US
Provisional Patent Application No 60/337,298, filed 5
November 2001, the entire disclosure of which is herein
incorporated by reference.

5

Technical Field

The present invention is within the field of
urology. More specifically, it is generally based on the
use of antimuscarinic agents for the treatment of urinary
10 disorders, said antimuscarinic agents being administered
by inhalation or insufflation.

Background of the Invention

Urinary disorders and symptoms thereof include some
15 or all of the following: urgency, frequency,
incontinence, urine leakage, enuresis, dysuria,
hesitancy, and difficulty of emptying bladder. In
particular, urinary disorders include urinary
incontinence, caused by e.g. unstable or overactive
20 urinary bladder.

A substantial part (5-10%) of the adult population
suffers from urinary incontinence, and the prevalence,
particularly of so-called urge incontinence, increases
with age. The symptoms of an unstable or overactive
25 bladder comprise urge incontinence, urgency and urinary
frequency. It is assumed that unstable or overactive
bladder is caused by uncontrolled contractions of the
bundles of smooth muscle fibres forming the muscular coat
of the urinary bladder (the detrusor muscle) during the
30 filling phase of the bladder. These contractions are
mainly controlled by cholinergic muscarinic receptors,
and the pharmacological treatment of unstable or

overactive bladder has been based on muscarinic receptor antagonists.

The reason why the bladder muscle contracts inappropriately is unclear in many cases. For some people 5 it may be due to a problem with the nerve signals that run from the brain to the bladder. Sometimes minor nerve damage is caused by surgery or childbearing. This muscle squeezes or contracts more often than normal and at inappropriate times. Instead of staying at rest as urine 10 fills the bladder, the detrusor contracts while the bladder is filling with urine. This causes a person to feel a sudden and sometimes overwhelming urge to urinate even when the bladder is not full.

US Patent 5,382,600 discloses 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, with the generic name of tolterodine, as being useful to treat urinary incontinence. H Postlind et al, Drug Metabolism and Disposition, 26(4): 289-293 15 (1998) discloses that tolterodine is a muscarinic receptor antagonist. It is presently being sold in a number of different countries for treatment of urinary incontinence under the name Detrol®, marketed by 20 Pharmacia. When tolterodine is used to treat urinary incontinence it is administered perorally as a tablet. The major, active metabolite of tolterodine is the 5-hydroxymethyl derivative of tolterodine. 25

US Patent 5,559,269 and H Postlind et al, Drug Metabolism and Disposition, 26(4): 289-293 (1998) 30 disclose hydroxytolterodine. US Patent 5,559,269 discloses this compound as being useful to treat urinary incontinence. Pharmacol. Toxicol., 81: 169-172 (1997) discloses that hydroxytolterodine has antimuscarinic activity. The international patent application WO 35 02/34245 discloses the use of tolterodine for treating asthma, COPD, and allergic rhinitis.

The international patent application WO 98/43942 discloses therapeutically active diarylpropylamines, which have favorable anticholinergic properties, and which can be used for the treatment of disorders related 5 to urinary incontinence.

US Patent 6,124,354 discloses 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate and its use in treating urinary incontinence and irritable bowel syndrome (see Example 99). Can. J. Chem., 10 40: 1909-1916 (1962) refers to this compound as a potential antidote for treatment of anticholinesterase poisoning. J. Am. Chem. Soc., 69: 2902-2906 (1947), while not mentioning the diisopropylamino compound but a diethylamino analog, discloses that the diethylamino 15 compound has antispasmolytic action against acetylcholine.

While efficiently relieving urinary incontinence in affected patients, the above-mentioned commercially available compounds do not provide their effects 20 instantly upon administration thereof to the patient. Since urinary disorder symptoms often have a rapid onset, it is desirable to relieve the symptoms instantly.

The currently marketed administration form of tolterodine is film-coated tablets containing 1 mg, 2 mg 25 or 4 mg of tolterodine L-tartrate for release in the gastrointestinal tract. Consumers constantly require alternative delivery forms, especially when the need for medicament treatment is urgent and/or when the patient has an active life-style.

Hence, known treatments are insufficient to certain 30 groups of patients, which demand a more flexible treatment to meet their active way of life.

There is a need for new delivery forms of 35 antimuscarinic agents for treatment of urinary disorders, which delivery forms possess properties such that the mentioned problems can be overcome.

Summary of the Invention

For these and other purposes, it is an object of the present invention to provide a method of treating urinary disorder in a mammal, including man, which method brings instant relief from symptoms arising from said urinary disorder.

It is also an object of the present invention to provide a method of treating urinary disorder in a mammal, including man, which method involves alternative delivery forms that are particularly suitable for urgent or acute treatment of symptoms.

It is an object of the present invention to provide a method of treating urinary disorder in a mammal, including man, which method is compatible with an active life-style.

It is a further object of the present invention to provide a pharmaceutical composition for treating urinary disorder in a mammal, including man, which can bring instant relief from symptoms arising from said urinary disorder.

It is also an object of the present invention to provide a pharmaceutical composition for treating urinary disorder in a mammal, including man, which is appropriate for alternative delivery forms being particularly suitable for urgent or acute treatment of symptoms.

It is an object of the present invention to provide a pharmaceutical composition for treating urinary disorder in a mammal, including man, use of which is compatible with an active life-style.

Another object of the present invention is to provide a novel use of an agent active against urinary disorder for the manufacture of a medicament for therapeutical treatment of urinary disorders, which medicament can bring instant relief from symptoms arising from said urinary disorder.

It is also an object of the present invention to provide a novel use of an agent active against urinary disorder for the manufacture of a medicament for therapeutical treatment of urinary disorders, which 5 medicament is appropriate for alternative delivery forms that are particularly suitable for urgent or acute treatment of symptoms.

Yet another object of the present invention is to provide a novel use of an agent active against urinary 10 disorder for the manufacture of a medicament for therapeutical treatment of urinary disorders, which medicament is compatible with an active life-style.

For these and other objects which will be evident from the following disclosure, the present invention 15 provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed 20 by inhalation or insufflation.

The invention is based on the insight that antimuscarinic agents are rapidly distributed to the systemic circulation upon delivery via inhalation or insufflation, thus providing their effects instantly at 25 target organs, such as the smooth muscles regulating emptying of the urinary bladder.

In one preferred embodiment of the method according to the invention, said disorder is unstable or overactive urinary bladder.

30 In a preferred embodiment of the method according to the invention, said disorder is urinary incontinence.

In another preferred embodiment of the method according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is administered as an aerosol 35 formulation.

In yet another preferred embodiment of the method according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is administered as a powder formulation.

5 In a preferred embodiment of the method according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

10 In a more preferred embodiment of the method according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

15 In a more preferred embodiment of the method according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

20 In the most preferred embodiment of the method according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

25 In a preferred embodiment of the method according to the invention, the administered amount of said antimuscarinic agent is from about 0.05 mg to about 12 mg.

30 In a more preferred embodiment of the method according to the invention, the administered amount of said antimuscarinic agent is from about 0.1 to about 6 mg.

35 In the most preferred embodiment of the method according to the invention, the administered amount of said antimuscarinic agent is from about 0.2 to about 5 mg.

Furthermore, the present invention provides a pharmaceutical composition for treating urinary disorder in a mammal, including man, which is in the form of an inhalable or insufflable preparation and comprises a 5 therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor.

In one preferred embodiment of the composition 10 according to the invention, said disorder is unstable or overactive urinary bladder.

In a preferred embodiment of the composition according to the invention, said disorder is urinary incontinence.

15 In another preferred embodiment of the composition according to the invention, said composition is an aerosol formulation.

In yet another preferred embodiment of the 20 composition according to the invention, said composition is a powder formulation.

In one preferred embodiment of the composition according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and 25 arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the composition according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine, 30 hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the composition according to the invention, said antimuscarinic agent is 35 selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

In the most preferred embodiment of the composition according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

5 In a preferred embodiment of the composition according to the invention, said antimuscarinic agent is present in an amount of from about 0.05 mg to about 12 mg, preferably from about 0.1 to about 6 mg, and more preferably from about 0.2 to about 5 mg.

10 The present invention also provides a novel use of an antimuscarinic agent, or solvate or prodrug thereof, for the manufacture of an inhalable or insufflable medicament for therapeutical treatment of urinary disorders.

15 In one preferred embodiment of the use according to the invention, said disorder is unstable or overactive urinary bladder.

In a preferred embodiment of the use according to the invention, said disorder is urinary incontinence.

20 In another preferred embodiment of the use according to the invention, said medicament is an aerosol formulation.

25 In yet another preferred embodiment of the use according to the invention, said medicament is a powder formulation.

In a preferred embodiment of the use according to the invention, said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

30 In a more preferred embodiment of the use according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-

phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

In a more preferred embodiment of the use according to the invention, said antimuscarinic agent is selected 5 from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

In the most preferred embodiment of the use according to the invention, said antimuscarinic agent is selected from the group consisting of tolterodine and 10 tolterodine L-tartrate.

Brief Description of the Drawings

Figure 1 is a diagram showing the plasma concentration (ng/ml) of tolterodine with time (hours) 15 upon systemic and local administration (aerosol) in mice.

Figure 2 is a diagram showing the plasma concentration (ng/ml) of tolterodine with time (hours) upon local administration (aerosol) of various amounts in mice.

20 Figure 3 is a diagram showing the variation of serum concentration (nmol/l) of tolterodine and its active metabolite with time (hours) during 9 hours upon administration of tolterodine perorally through a 2 mg tablet in human patients.

25

Description of the Invention

The present invention involves the use of antimuscarinic agents to treat urinary disorders, such as 30 unstable or overactive urinary bladder.

Overactive urinary bladder encompasses various urinary disorders, including overactive urinary bladder detrusor instability, detrusor hyperreflexia, urge 35 incontinence, urgency and urinary frequency and LUTS (Lower Urinary Tract Symptoms giving obstructive urinary symptoms such as slow urination, dribbling at the end of urination, inability to urinate and/or the need to strain

to urinate at an acceptable rate or irritate symptoms such as frequency an/ or urgency).

Other conditions are also included, which give rise to urinary frequency, urgency and/or urge incontinence.

5 Overactive bladder disorders also include nocturia and mixed incontinence. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including
10 spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder
15 cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis.

The method of the present invention is used to treat mammals, including man. It is preferred that the mammal is a human.

20 Upon traditional tablet administration of antimuscarinic agents to treat urinary disorders, the plasma concentration thereof increases rather slowly, peaking after 1-2 hours. The antimuscarinic agents are often metabolized by the liver following oral dosing.
25 According to the present invention, administration of antimuscarinic agents to patients for treatment of urinary disorders can advantageously be performed via inhalation or insufflation. Thereby, the antimuscarinic agents instantly gain access to the systemic circulation and can affect target tissues, such as the smooth
30 musculature surrounding the urinary tract.

The compositions according to the invention can be made up in solid or liquid form, such as powders, sterile solutions, suspensions or emulsions, and the like.

35 The antimuscarinic agents of the present invention are administered by inhalation or insufflation. The

inhalation or insufflation is preferably by either an aerosol or a powder.

The method and the antimuscarinic agents and compositions of the present invention are useful for the 5 treatment of unstable or overactive urinary bladder, e.g. urinary incontinence.

The dosage of the specific antimuscarinic agent will vary depending on its potency, the mode of administration, the age and weight of the patient and the 10 severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 4 mg per kg of body weight, administered singly or multiply in doses e.g. from about 0.05 mg to about 200 mg each. A clinically effective amount of antimuscarinic agents is 15 from about 0.05 mg to about 12 mg. It is preferred that the effective amount is from about 0.1 to about 6 mg; it is more preferred that the effective amount is from about 0.2 to about 5 mg.

The dosage form for inhalation can be an aerosol. 20 The minimum amount of an aerosol delivery is about 0.2 ml and the maximum aerosol delivery is about 5 ml. The concentration of the antimuscarinic agents may vary as long as the total amount of spray delivered is within the about 0.2 to about 5 ml amount and it delivers an 25 effective amount. It is well known to those skilled in the art that if the concentration is higher, one gives a smaller dose to deliver the same effective amount.

The non-active ingredient or carrier can be just (sterile) water with the pH adjusted to where the active 30 pharmaceutical agent is very soluble. It is preferred that the pH be at or near 7. Alternatively and preferably, the non-active carrier agent should be physiological saline with the pH adjusted appropriately. Aerosols for inhalation of various pharmaceutical agents 35 are well known to those skilled in the art, including many aerosols for treating asthma.

Alternatively, the dosage form for inhalation can be a powder. Powders for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many powders for treating asthma. When 5 the dosage form is a powder, the antimuscarinic agent can be administered in pure form or diluted with an inert carrier. When an inert carrier is used, the antimuscarinic agent is compounded such that the total amount of powder delivered delivers an "effective amount" 10 of the agent. The actual concentration of the agent may vary. If the concentration is lower, then more powder must be delivered; if the concentration is higher, less total material must be delivered to provide an effective amount of the agent.

15 The carriers may be of any inert material, organic or inorganic, suitable for administration via inhalation or insufflation, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium 20 stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavoring agents, buffers, and the like.

25 Various devices are on the market for administering powders for inhalation for asthma, and these devices are suitable for administering the antimuscarinic agents of the present invention.

30 Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The pharmaceutically acceptable salts are preferred over the corresponding free amines since they produce compounds that are more water soluble and more crystalline. The preferred pharmaceutically acceptable salts include salts of the 35 following acids: tartaric, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, citric, methanesulfonic,

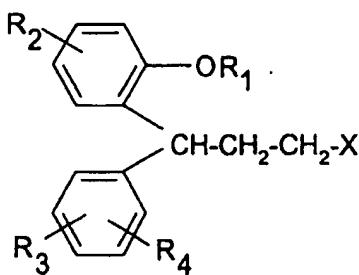
$\text{CH}_3\text{-(CH}_2\text{)}_n\text{-COOH}$ where n is 0 through 4, $\text{HOOC-(CH}_2\text{)}_n\text{-COOH}$, where n is as defined above, HOOC-CH=CH-COOH , $\phi\text{-COOH}$. For other acceptable salts, see *Int. J. Pharm.*, 33: 201-217 (1986).

5 An exemplary class of antimuscarinic agents which may be used as active ingredients in the present invention comprises the arylcycloalkane carboxylic esters disclosed in US-6,124,354 (the entire disclosures of which are incorporated by reference herein).

10 An exemplary specific antimuscarinic agent is 2-[bis(1-methylethyl)amino]ethyl-1-phenylcyclopentanecarboxylate, also known as 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as metabolites, prodrug forms and

15 pharmaceutically acceptable salts thereof.

Another exemplary class of antimuscarinic agents which may be used as active ingredients in the present invention comprises the 3,3-diphenylpropylamines disclosed in US-A-5,382,600, US-A-5,559,269 and US-A-20 5,686,464 (the entire disclosures of which are incorporated by reference herein) and having the general formula:



25 wherein R_1 signifies hydrogen or methyl; R_2 , R_3 and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, hydroxymethyl, carbamoyl, sulphamoyl or halogen; and X represents a tertiary amino group $-\text{NR}_5\text{R}_6$, wherein R_5 and R_6 signify non-aromatic hydrocarbyl groups, which may be

30 the same or different, especially C_{1-6} -alkyl or

adamantyl, and which together contain at least three, preferably at least four carbon atoms, and each of which may carry a hydroxy substituent, and wherein R₅ and R₆ may form a ring together with the amine nitrogen,

5 preferably a non-aromatic ring having no heteroatom other than the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

10 Exemplary specific compounds include tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, as well as the corresponding (S)-enantiomer, the racemate and the active 5-hydroxymethyl metabolites, solvates, prodrug forms and pharmaceutically acceptable salts thereof.

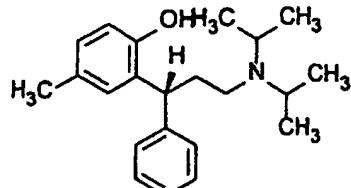
Useful analogues to the above compounds are disclosed in WO 98/43942 (the full disclosure of which is incorporated by reference herein).

20 Specifically, the compositions according to the present invention have proved to be very suitable for administering the above-mentioned drug tolterodine and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer; i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

30 Tolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol, also known as (R)-N,N-

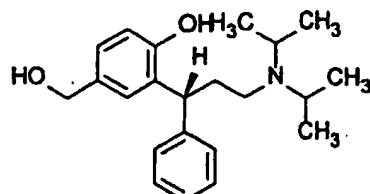
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diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, a compound of the formula:



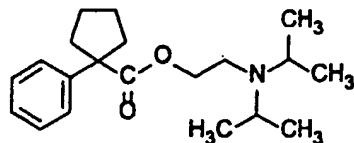
(R)-stereoisomer

Hydroxytolterodine refers to 2-[(1R)-3-5 (diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol, a compound of the formula:



(R)-stereoisomer

2-[bis(1-methylethyl)amino]ethyl-1-phenylcyclopentanecarboxylate, also known as 2-10 (diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, refers to a compound of the formula:



"Antimuscarinic agents" refer to muscarinic receptor antagonists. Examples of antimuscarinic agents include, 15 but are not limited to, tolterodine, hydroxytolterodine, 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, propiverine, oxybutynin, trospium, darifenacin, temiverine, and ipratropium.

Propiverine is 1-methyl-4-piperidyl .alpha..alpha.-20 diphenyl-.alpha..-(n-propoxy)acetate and is disclosed in East German Patent 106,643 and in CAS 82-155841s (1975). Oxybutynin is 4-(diethylamino)-2-

butynylalphaphenylcyclohexaneglycolate and is disclosed in UK Patent 940,540. Trospium is 3alpha-hydroxyspiro[1alphaH,5alphaH-nortropane-8,1'pyrrolidinium]chloride benzilate and is disclosed in 5 US Patent 3,480,623. Darifenacin is 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-alpha, alpha-diphenyl-, and is disclosed in US Patent 5,096,890. Temiverine is benzeneacetic acid, .alpha.-cyclohexyl-.alpha.-hydroxy-, 10 4-(diethylamino)-1,1-dimethyl-2-butynyl ester and is disclosed in US Patent 5,036,098. Ipratropium is 8-isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337.

15 "Physiological saline" generally refers to a 0.9% aqueous sodium chloride solution.

20 "Pharmaceutically acceptable" refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

25 Analogously, "inhalably acceptable" and "insufflably acceptable", respectively, refer to properties and/or substance which are pharmaceutically acceptable and also suitable for use via inhalation and insufflation, respectively.

Examples

30 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various antimuscarinic agent and/or perform the various 35 methods of the invention and are to be construed as merely illustrative, and not limitations of the preceding

disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

5

Example 1. Pharmacokinetic comparison of systemic and local (aerosol) administration, respectively, of tolterodine

Female BALB/c mice, weight range 19-22 g, were 10 obtained from Charles River Laboratories (Kingston, NC). They received food and water *ad libitum*. All procedures in these studies were in compliance with the Animal Welfare Act Regulation, 9CFR Parts 1 and 2, Publication (NIH) 85-23, 1985.

15 Tolterodine L-tartrate, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-tartrate, for intraperitoneal administration was prepared in sterile 0.9% NaCl.

20 Tolterodine L-tartrate for aerosol administration was prepared in sterile phosphate buffer solution at a concentration of 1.0 mg/ml.

25 Mice were placed in a carousel-style, nose only, exposure chamber and allowed to inhale aerosols of tolterodine for five minutes, using an ICN SPAG-2 nebulizer. This nebulizer generates a mean aerosol particle size of 1.3 microns at a rate of approximately 0.25 ml/minute.

Thus, mice received tolterodine either by aerosol generated from a 1 mg/ml solution for five minutes or by 30 intraperitoneal (i.p.) injection at a dose of 3 mg/kg. Blood samples were taken via cardiac puncture under isoflurane anesthesia at 5, 15, 30, 60, 120, and 240 minutes after i.p. treatment and at 2.5, 5, 15, 30, 60, and 120 minutes after aerosol drug treatment.

The samples were collected in tubes containing EDTA and centrifuged at 12000 x g for four minutes. Plasma was removed and stored at -70 °C until assay.

Plasma samples were extracted via a liquid/liquid extraction technique. Plasma levels for tolterodine were determined by ESI-LC/MS/MS using a PE SCIEX API 3000 mass spectrometer in positive ion mode. Chromatographically, the analyte and internal standard were resolved on a Zorbax ACE Phenyl column(2.1 x 50mm) using a gradient elution. The total analysis time was 4 minutes with a limit of quantitation of 100pg/mL.

Plasma concentrations of tolterodine following 3 mg/kg i.p. injection and following 1 mg/ml aerosol exposure (inhalation) are summarized in Figure 1.

15 Example 2. Aerosol administration of different amounts of tolterodine

Female BALB/c mice, weight range 19-22 g, were obtained from Charles River Laboratories (Kingston, NC). 20 They received food and water *ad libitum*. All procedures in these studies were in compliance with the Animal Welfare Act Regulation, 9CFR Parts 1 and 2, Publication (NIH) 85-23, 1985.

25 Tolterodine L-tartrate for aerosol administration was prepared in sterile phosphate buffer solution at concentrations of 0.1, 0.5, and 1.0 mg/ml.

As described in Example 1, mice were exposed to aerosols of tolterodine generated from either 0.1, 0.5, or 1.0 mg/ml solutions. The duration of aerosol treatment 30 was five minutes. Blood samples were collected via cardiac puncture at 2.5, 5, 15, 30, 60, and 120 minutes following the end of the drug nebulization period.

The samples from were collected in tubes containing EDTA and centrifuged at 12000 x g for four minutes. 35 Plasma was removed and stored at -70 °C until assay.

Plasma samples were extracted and plasma levels for tolterodine were determined as described in Example 1.

Figure 2 shows plasma concentrations of tolterodine L-tartrate following inhalation of nebulized solutions at 5 0.1, 0.5, or 1.0 mg/mL. Plasma levels for the 0.1 mg/mL concentration were at or below detection limits. Clearly, tolterodine is rapidly absorbed into the circulation.

10 Example 3. Comparative pharmacokinetic study of oral administration of tolterodine

This example illustrates the systemic distribution in man of perorally administrated prior art tolterodine tablets.

15 In 30 human patients with overactive bladder, the pharmacokinetic effects were determined of a film-coated tablet containing 2 mg of tolterodine L-tartrate. Serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) were measured over time.

20 Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6 and 9 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated 25 assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129-1136).

Figure 3 shows the obtained variation with time of 30 the sum of the unbound concentrations of tolterodine and 5-HM for the administration of a 2 mg tablet.

It is apparent that the patterns of blood 35 concentrations of tolterodine and its active metabolite are altered upon aerosol administration thereof (examples 1 and 2, fig 1 and 2), when compared to prior art oral

20

administration (example 3, fig 3). Aerosol administration (fig 1 and 2) produces within a few minutes a distinct and instant rise in tolterodine plasma concentration, similar in pattern to what is seen upon intraperitoneal 5 injection (fig 1). In contrast, oral administration (fig 3) results in slower uptake of tolterodine into the circulation, wherein a maximum blood concentration is reached in the range of one hour, and a concomitant prolonged presence of tolterodine in the circulation.

10

Claims

1. A method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation.
2. A method according to claim 1, wherein said disorder is unstable or overactive urinary bladder.
3. A method according to claim 1, wherein said disorder is urinary incontinence.
4. A method according to claim 1, wherein said antimuscarinic agent, or solvate or prodrug thereof, is administered as an aerosol formulation.
5. A method according to claim 1, wherein said antimuscarinic agent, or solvate or prodrug thereof, is administered as a powder formulation.
6. A method according to any one of claims 1-5, wherein said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.
7. A method according to claim 6, wherein said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.
8. A method according to claim 7, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

9. A method according to claim 8, wherein said antimuscarinic agent is selected from the group consisting of tolterodine and tolterodine L-tartrate.

10. A method according to claim 1, wherein the 5 administered amount of said antimuscarinic agent is from about 0.05 mg to about 12 mg.

11. A method according to claim 1, wherein the administered amount of said antimuscarinic agent is from about 0.1 to about 6 mg.

10 12. A method according to claim 1, wherein the administered amount of said antimuscarinic agent is from about 0.2 to about 5 mg.

13. A pharmaceutical composition for treating urinary disorder in a mammal, including man, which is in 15 the form of an inhalable or insufflable preparation and comprises a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, together with an inhalably or insufflably acceptable carrier or diluent therefor.

20 14. A composition according to claim 13, wherein said disorder is unstable or overactive urinary bladder.

15. A composition according to claim 13, wherein said disorder is urinary incontinence.

25 16. A composition according to claim 13, which is an aerosol formulation.

17. A composition according to claim 13, which is a powder formulation.

18. A composition according to any one of claims 13- 30 17, wherein said antimuscarinic agent, or solvate or prodrug thereof, is selected from the group consisting of 3,3-diphenylpropylamines and arylcycloalkane carboxylic esters, and inhalably or insufflably acceptable salts thereof.

19. A composition according to claim 18, wherein 35 said antimuscarinic agent is selected from the group consisting of tolterodine, hydroxytolterodine, and 2-

(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

20. A composition according to claim 19, wherein
5 said antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

21. A composition according to claim 20, wherein
said antimuscarinic agent is selected from the group
10 consisting of tolterodine and tolterodine L-tartrate.

22. A composition according to claim 13, wherein
said antimuscarinic agent is present in an amount of from
about 0.05 mg to about 12 mg.

23. A composition according to claim 13, wherein
15 said antimuscarinic agent is present in an amount of from
about 0.1 to about 6 mg.

24. A composition according to claim 13, wherein
said antimuscarinic agent is present in an amount of from
about 0.2 to about 5 mg.

20 25. Use of an antimuscarinic agent, or solvate or
prodrug thereof, for the manufacture of an inhalable or
insufflable medicament for therapeutical treatment of
urinary disorders.

26. Use according to claim 25, wherein said disorder
25 is unstable or overactive urinary bladder.

27. Use according to claim 25, wherein said disorder
is urinary incontinence.

28. Use according to claim 25, wherein said
medicament is an aerosol formulation.

30 29. Use according to claim 25, wherein said
medicament is a powder formulation.

30. Use according to any one of claims 25-29,
wherein said antimuscarinic agent, or solvate or prodrug
thereof, is selected from the group consisting of 3,3-
35 diphenylpropylamines and arylcycloalkane carboxylic

esters, and inhalably or insufflably acceptable salts thereof.

31. Use according to claim 30, wherein said antimuscarinic agent is selected from the group 5 consisting of tolterodine, hydroxytolterodine, and 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, as well as inhalably or insufflably acceptable salts thereof.

32. Use according to claim 31, wherein said 10 antimuscarinic agent is selected from the group consisting of tolterodine and inhalably or insufflably acceptable salts thereof.

33. Use according to claim 32, wherein said antimuscarinic agent is selected from the group 15 consisting of tolterodine and tolterodine L-tartrate.

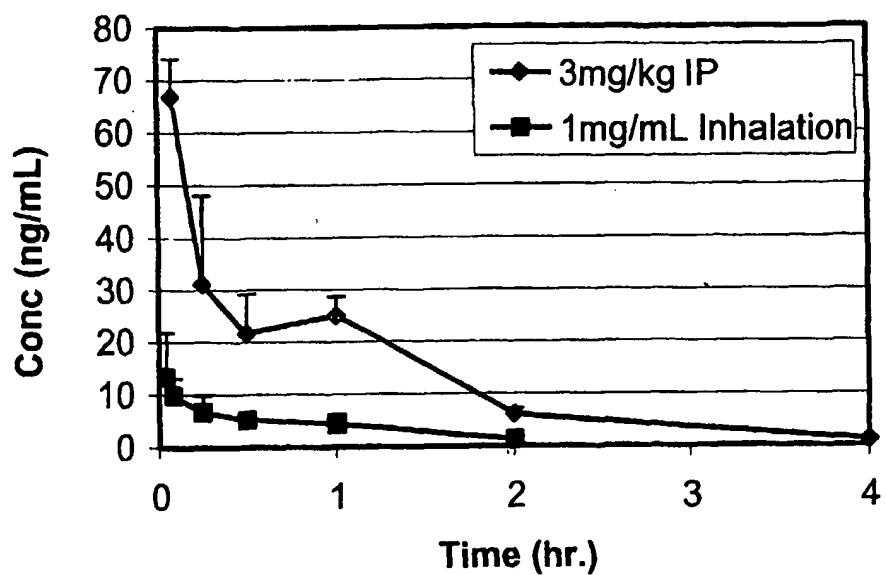


FIGURE 1

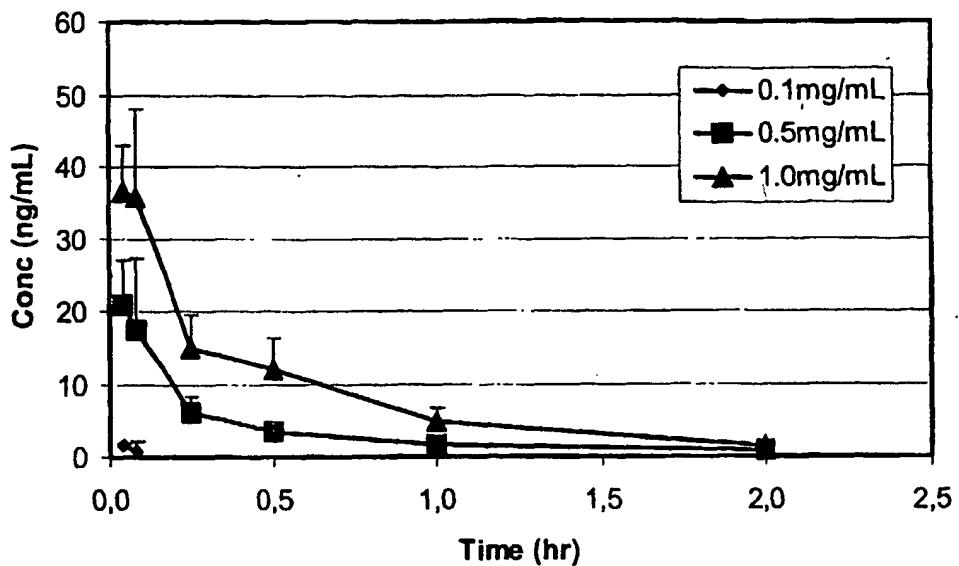


FIGURE 2

5

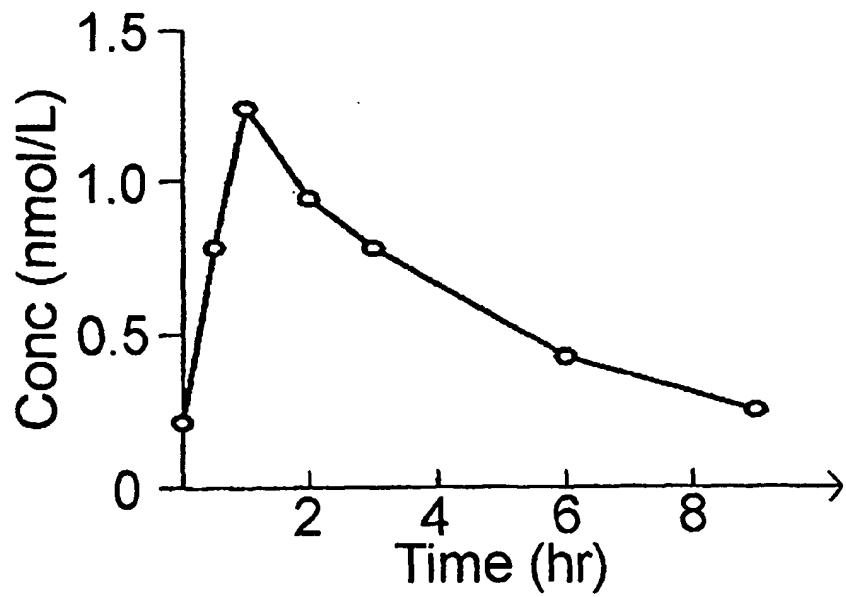


FIGURE 3

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(74) Agents: KOZLOWSKI, Holly, D., et al.; Dinsmore & Shohl LLP, 1900 Chemed Center, 255 East Fifth Street, Cincinnati, OH 45202 (US).

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(71) Applicant (for all designated States except US): PHARMACIA & UPJOHN COMPANY [US/US]; 100 Route 206 North, Peapack, NJ 07977 (US).

(88) Date of publication of the international search report: 26 February 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 2003/039464 A3

(54) Title: ANTIMUSCARINIC AEROSOL

(57) Abstract: The present invention concerns the use of antimuscarinic agents for the treatment of urinary disorders. The invention provides a method of treating urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of an antimuscarinic agent, or solvate or prodrug thereof, said administration being performed by inhalation or insufflation.

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A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	A61K31/00	A61K31/137	A61K31/216	A61K9/12	A61P13/00
	A61P13/10				

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7	A61K	A61P
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03 002059 A (BRIDGE PHARMA INC) 9 January 2003 (2003-01-09) abstract page 5, last paragraph; claims 1-15 -----	1-6, 10-18, 22-30
P,X	WO 02 17907 A (SHERRATT AMANDA J ; THERAMAX INC (US); HOUDI ABDULGHANI A (US)) 7 March 2002 (2002-03-07) the whole document -----	1-5, 10-17, 22-29
P,X	WO 02 34245 A (SUNDQUIST STAFFAN ; PHARMACIA AB (SE); GILLBERG PER GORAN (SE); UPJ) 2 May 2002 (2002-05-02) the whole document ----- -/-	13-24

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 July 2003

Date of mailing of the international search report

-4.11.2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hoff, P.

INTERNATIONAL SEARCH REPORT

Int Application No
PCT/US 02/35335

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 03067 A (ABERG GUNNAR) 29 January 1998 (1998-01-29) abstract page 4, paragraph 2; claims 1,2,4,6; examples ----- WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26 May 1994 (1994-05-26) cited in the application abstract page 6, line 36 - page 7, line 3 page 7, line 24 - line 28; claims; examples ----- WO 96 23492 A (SEPRACOR INC) 8 August 1996 (1996-08-08) abstract; claims 1-3,7,8; examples ----- US 5 736 577 A (MCCULLOUGH JOHN R ET AL) 7 April 1998 (1998-04-07) abstract column 2, line 55 - line 59 column 3, line 48 - line 52; claims 1,4; examples ----- "MARTINDALE, The complete drug reference" 2000, PHARMACEUTICAL PRESS , XP002246330 page 453 - page 454 page 754 - page 755 page 757 ----- EP 0 325 571 A (KABIVITRUM AB) 26 July 1989 (1989-07-26) cited in the application abstract page 6, line 59 - line 63; claims; example 22 -----	1-33 1-33 1-5, 10-17, 22-29 1-5, 10-17, 22-29 13-17, 22-24 1-33

INTERNATIONAL SEARCH REPORT

.....ational application No.
PCT/US 02/35335

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-7, 10-19, 22-31 (all partially), 8, 9, 20, 21, 32, 33

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

Present claims 1-5,10-17,22-29 relate to a compound defined by reference to a desirable characteristic or property, namely "antimuscarinic agent".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, present claims 1-6,13-18,25-30 relate to an extremely large number of possible compounds (in terms of 3,3-diphenylpropylamines, arylcycloalkane carboxylic esters, prodrug). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. Again, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds tolterodine and hydroxytolterodine, with due regard to the general idea underlying the present invention.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims:

1-7(partially),8,9,10-19(partially),20,
21,22-31(partially),32,33

Use of the antimuscarinic agents tolterodine and
hydroxytolterodine for treating urinary disorders by
inhalation or insufflation and composition thereof

2. claims: 1-7(partially),10-19(partially),22-31(partially)

Use of the antimuscarinic agent
2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate
for treating urinary disorders by inhalation or insufflation
and composition thereof

INTERNATIONAL SEARCH REPORT

Inte
al Application No
PCT/US 02/35335

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 03002059	A	09-01-2003	US 2003027856 A1		06-02-2003
			WO 03002059 A2		09-01-2003
WO 0217907	A	07-03-2002	US 2002161044 A1		31-10-2002
			AU 8839501 A		13-03-2002
			EP 1333825 A1		13-08-2003
			WO 0217907 A1		07-03-2002
			US 2003191183 A1		09-10-2003
WO 0234245	A	02-05-2002	AU 1296202 A		06-05-2002
			CA 2422901 A1		02-05-2002
			EP 1330241 A2		30-07-2003
			WO 0234245 A2		02-05-2002
			US 2002161054 A1		31-10-2002
WO 9803067	A	29-01-1998	AU 728395 B2		11-01-2001
			AU 3725997 A		10-02-1998
			CA 2259012 A1		29-01-1998
			EP 0924983 A1		30-06-1999
			JP 2000515525 T		21-11-2000
			WO 9803067 A1		29-01-1998
			US 6310103 B1		30-10-2001
WO 9411337	A	26-05-1994	AT 164828 T		15-04-1998
			AU 672458 B2		03-10-1996
			AU 5438094 A		08-06-1994
			CA 2148827 A1		26-05-1994
			DE 69317898 D1		14-05-1998
			DE 69317898 T2		15-10-1998
			DK 667852 T3		11-01-1999
			EP 0667852 A1		23-08-1995
			ES 2117155 T3		01-08-1998
			FI 952179 A		05-05-1995
			HK 1006349 A1		19-02-1999
			HU 72742 A2		28-05-1996
			JP 3343256 B2		11-11-2002
			JP 8503208 T		09-04-1996
			NO 951775 A		05-05-1995
			WO 9411337 A1		26-05-1994
			US 5559269 A		24-09-1996
			US 5686464 A		11-11-1997
WO 9623492	A	08-08-1996	US 5532278 A		02-07-1996
			US 5677346 A		14-10-1997
			AT 196252 T		15-09-2000
			AU 706741 B2		24-06-1999
			AU 4966496 A		21-08-1996
			BR 9607001 A		28-10-1997
			CA 2211400 A1		08-08-1996
			CZ 9702421 A3		17-12-1997
			DE 69610290 D1		19-10-2000
			DE 69610290 T2		29-03-2001
			DK 806948 T3		18-12-2000
			EP 0806948 A1		19-11-1997
			ES 2150663 T3		01-12-2000
			FI 973163 A		30-09-1997
			GR 3034974 T3		28-02-2001
			HU 9800794 A2		28-07-1998

INTERNATIONAL SEARCH REPORT

 Inter. Application No
 PCT/US 02/35335

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9623492	A	JP NO NZ PL PT RU SK WO US	11511730 T 973516 A 303372 A 321498 A1 806948 T 2181589 C2 103597 A3 9623492 A1 5736577 A	12-10-1999 07-08-1997 28-01-1999 08-12-1997 28-02-2001 27-04-2002 10-03-1999 08-08-1996 07-04-1998
US 5736577	A 07-04-1998	US AU AU BR CA CZ EP HU JP KR NO NZ PL RU SK WO AT AU AU BR CA CZ DE DE DK EP ES FI GR HU JP NO NZ PL PT RU SK WO US	5532278 A 732568 B2 3513797 A 9710031 A 2257121 A1 9804283 A3 0914113 A1 9903839 A2 2000513724 T 2000022194 A 985896 A 333282 A 330752 A1 2195276 C2 178698 A3 9800126 A1 196252 T 706741 B2 4966496 A 9607001 A 2211400 A1 9702421 A3 69610290 D1 69610290 T2 806948 T3 0806948 A1 2150663 T3 973163 A 3034974 T3 9800794 A2 11511730 T 973516 A 303372 A 321498 A1 806948 T 2181589 C2 103597 A3 9623492 A1 5677346 A	02-07-1996 26-04-2001 21-01-1998 10-08-1999 08-01-1998 16-06-1999 12-05-1999 28-03-2000 17-10-2000 25-04-2000 16-12-1998 23-06-2000 24-05-1999 27-12-2002 10-09-1999 08-01-1998 15-09-2000 24-06-1999 21-08-1996 28-10-1997 08-08-1996 17-12-1997 19-10-2000 29-03-2001 18-12-2000 19-11-1997 01-12-2000 30-09-1997 28-02-2001 28-07-1998 12-10-1999 07-08-1997 28-01-1999 08-12-1997 28-02-2001 27-04-2002 10-03-1999 08-08-1996 14-10-1997
EP 0325571	A 26-07-1989	AT AU AU CA DE DK EP EP	65990 T 635493 B2 2932989 A 1340223 C 68900180 D1 172590 A 0325571 A1 0354234 A1	15-08-1991 25-03-1993 11-08-1989 15-12-1998 12-09-1991 19-07-1990 26-07-1989 14-02-1990

INTERNATIONAL SEARCH REPORT

Intel Application No
PCT/US 02/35335

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0325571	A	ES	2029384 T3	01-08-1992
		FI	109900 B1	31-10-2002
		GR	3002854 T3	25-01-1993
		HK	64494 A	15-07-1994
		HU	58040 A2	28-01-1992
		HU	9400053 A3	30-01-1995
		JP	2664503 B2	15-10-1997
		JP	3503163 T	18-07-1991
		LU	90259 A9	16-09-1998
		NO	903085 A ,B,	11-07-1990
		WO	8906644 A1	27-07-1989
		US	5382600 A	17-01-1995